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An Enantioselective Total Synthesis of (+)-Peloruside A

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Peloruside A (**1**), a potent microtubule stabilizer that acts in a manner synergistic to that of paclitaxel, was first isolated in 2000 by Northcote and coworkers from a marine sponge of the Pelorus Sound in New Zealand.[1] The absolute stereochemistry of **1** was established in De Brabander's initial total synthesis in 2003,[2] and since then three other total syntheses have been reported.[3–5]

Herein, we describe a convergent total synthesis of peloruside A in which three different enantioenriched epoxides (**8**, **9**, and **11**, Figure 1) obtained using asymmetric catalytic methodologies serve as the key building blocks for the stereochemically complex macrocyclic framework. A second key strategic feature is a chiral catalyst-controlled diastereoselective hetero-Diels–Alder reaction for the construction of intermediate **7**. The application of direct catalyst control represents a complement to the previous synthetic approaches to peloruside A, which relied primarily on substrate- and auxiliary-based diastereocontrol to establish the relative and absolute stereochemical features of the natural product.[2–5]

Dissection of the seco ester form of peloruside A into fragments of roughly equal size and complexity suggested aldehyde **3** and enone **4** as potentially useful late-stage intermediates (Figure 1).[6] The synthesis of enone **4** began with a highly enantioselective Payne rearrangement of meso-epoxy diol **12**, available in one step from commercial cis-2,3-butenediol, to enantioenriched terminal epoxide **14** (Scheme 1).[7] This transformation was catalyzed by oligomeric cobalt salen catalyst **13**,[8] which establishes an equilibrium favoring terminal epoxide **14** over meso epoxide **12** in a 7:3 ratio. Epoxide **14** was unstable

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to purification, but protection as the primary silyl ether in situ and subsequent alkylation of the secondary alcohol provided the functionally-rich bis-protected epoxide **11** in good overall yield.[9]

Epoxide **11** was subjected to a one-pot vinyl cuprate addition/methylation, followed by ozonolysis to provide aldehyde **15** in 66% overall yield. In an analogous manner, enantiopure aldehyde **16** was obtained from racemic epoxide **9** via a high-yielding hydrolytic kinetic resolution (HKR)/vinylation/alkyation/ozonolysis sequence.

Aldehyde **15** was then engaged in a hetero-Diels–Alder (HDA) reaction with trioxy-substituted diene **10**, available in two steps from methyl benzyloxyacetate (see Supporting Information). Diene **10** proved highly sensitive to decomposition in the presence of strong Lewis acids, but cycloadditions catalyzed by (Schiff-base)chromium complexes were found to proceed cleanly. The degree of intrinsic substrate diastereocontrol was poor, as reaction with achiral chromium catalyst **17** afforded cycloadduct in 1:2 dr favoring the *undesired* isomer. However, the chiral chromium Schiff-base complex (1*R*,2*S*)-**18**[10] catalyzed formation of the desired product **7** in good yield and 7:1 dr favoring the *desired* isomer. Conversely, the enantiomeric catalyst (1*S*,2*R*)-**18** provided the undesired diastereomer in high (1:11) selectivity. This represents one of the most demanding applications reported to date of the application of catalyst **18** in an HDA reaction between stereochemically and functionally complex substrates.[11]

Hydrogenation of hetero-Diels–Alder adduct **7** took place diastereoselectively, and concomitant hydrogenolysis of the *O*-benzyl acetal provided **19** in 69% yield and in 10:1 dr.[12] Oxidation of lactol **19** and opening of the resulting lactone with *N*,*O*-dimethylamine hydrochloride afforded Weinreb amide **20**, which was protected as the secondary TBS ether. Addition of isopropenylmagnesium bromide occurred with cleavage of the C8 acetate ester to provide hydroxyenone **21**, which was purified chromatographically to >20:1 dr. The C8 hydroxyl group was then re-protected as the TBS ether to provide aldol coupling partner **4** (Scheme 3).

In the approach to aldehyde **3**, epoxide **8** was prepared in high ee from enyne **24**, available in two steps from commercial 3-pentyn-1-ol,[13] via a (salen)Mn-catalyzed epoxidation[14]/hydrolytic kinetic resolution (HKR) sequence.[15] Epoxide **8** was then opened stereospecifically and regioselectively at the propargylic position, and the resulting primary alcohol was protected as the triisopropylsilyl ether to provide alkyne **25** in 72% yield over two steps (Scheme 4). This strategy of opening a terminal epoxy-alkyne at the internal position with a simple Grignard reagent provides a concise and convenient method for the stereocontrolled synthesis of homopropargylic primary alcohols.

Silyl ether **25** was further elaborated to vinyl bromide **5** via a one-pot hydroboration/bromination/elimination/silyl-deprotection sequence (Scheme 4).[16] Protection of the resultant primary alcohol as the benzyl ether provided compound **5** in 69% overall yield from **25**.[17] This protecting-group exchange on the C20 hydroxyl proved advantageous because a large silyl protecting group was required for attaining high regioselectivity (9:1) in the hydroboration of compound **25**, while the presence of a benzyl protecting group led to improved diastereoselctivity in the addition of the vinyl lithium reagent derived from **5** into aldehyde **17**. In this manner, alcohol **26** was obtained in 5:1 dr and isolated in 64% yield following chromatographic purification. In contrast, analogous silyl-protected vinyl bromides (TIPS, TBDPS) led to the corresponding allylic alcohols in only 2:1 dr. Alcohol **26** was then protected as the paramethoxybenzyl ether, and the primary alcohol was selectively unmasked and oxidized with the Dess-Martin periodinane to provide aldehyde **3** in 58% yield over the 3 steps.

Enone **4** and aldehyde **3** were coupled via a reductive aldol reaction similar to that utilized in the Ghosh synthesis of peloruside A[4] to afford **2** in 1.7:1 dr. Despite the modest stereoselectivity in this step, **2** could be isolated in diastereomerically pure form and in 52% yield following chromatographic purification (Scheme 5). The primary TBS ether was then removed selectively using buffered HF·pyridine and the resulting alchol oxidized to provide aldehyde **27** in 74% yield over the 2 steps. Aldehyde **27** was then oxidized to the corresponding acid, and the crude reaction mixture was subjected to pH 7 buffered DDQ to cleave the C15 PMB ether and afford the macrolaconization substrate. The seco acid was subjected without purification to Yamaguchi conditions to provide macrolactone **28** in 52% yield for the 3 steps from aldehyde **27**. This macrolactonization strategy drew direct inspiration from the Evans approach to peloruside A employing a similarly protected seco acid,[5] wherein differentiation between free hydroxyl groups at C11 and C15 was also observed. Finally, the benzyl protecting group at the C20 hydroxyl was removed under transfer hydrogenolysis conditions, and a subsequent global deprotection of the remaining protecting groups under strongly acidic conditions[18] afforded (+)-peloruside A (**1**) in 57% isolated yield, with characterization data matching those reported for the natural product.[1]

This convergent synthesis of (+)-peloruside A required 20 steps in the longest linear sequence from commercially available materials. The approach relies on the availability of both simple (e.g. **8** and **9**) and relatively complex (i.e., **11**) terminal epoxides via (salen)Co-catalyzed ring-opening reactions, and on chiral catalyst-induced diastereocontrol in a key hetero-Diels–Alder cycloaddition reaction between advanced intermediates. The route provides a useful illustration of the applicability of modern asymmetric catalytic methods in the total synthesis of stereochemically complex polyketides.

Experimental Section

Full experimental details are provided as Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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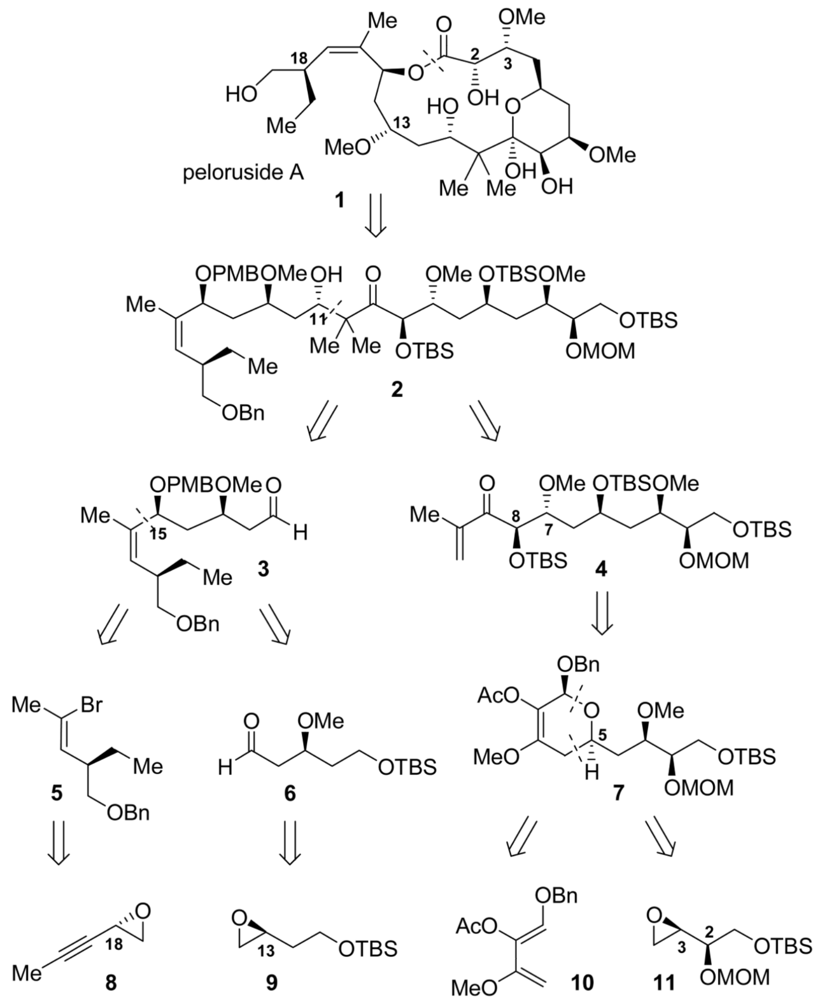
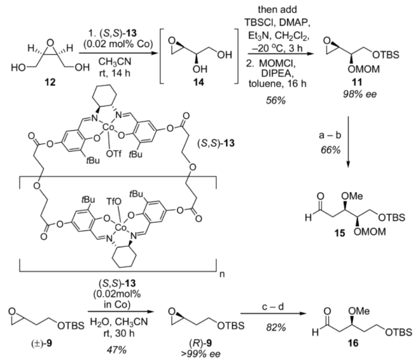
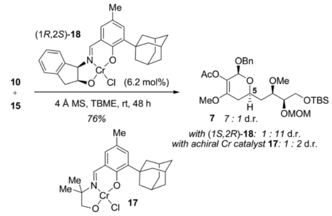


Figure 1.
Retrosynthetic analysis of peloruside A



Scheme 1.

Asymmetric Payne rearrangement and elaboration. Reagents and conditions: a) CuBr (10 mol%), vinyl magnesium bromide, −40 °C, 2 h; then HMPA, Me_2SO_4, rt, 48 h; b) O_3, CH_2Cl_2, −78 °C; then PPh_3, rt, 3 h; c) CuBr (10 mol%), vinyl magnesium bromide, −40 °C, 2 h; then HMPA, Me_2SO_4, 4 °C, 48 h; d) O_3, CH_2Cl_2, −78 °C; then PPh_3, rt, 3 h. DIPEA=diisopropylethylamine, TBSCl=*t*-butyldimethylsilyl chloride, MOMCl=methoxymethyl chloride, HMPA= hexamethylphosphoramidite, PPh_3=triphenylphosphine.



Scheme 2.
Diastereoselective hetero-Diels–Alder Reaction.

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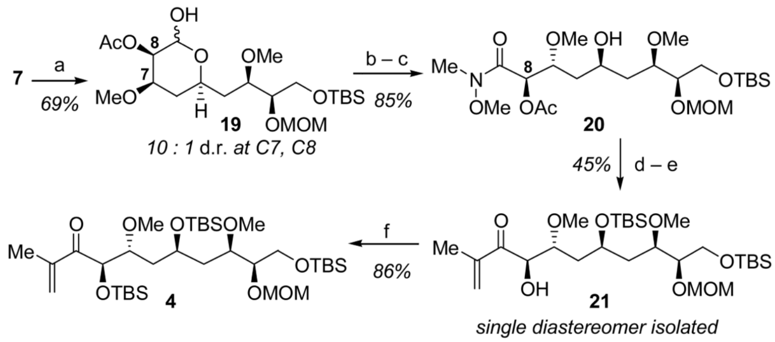
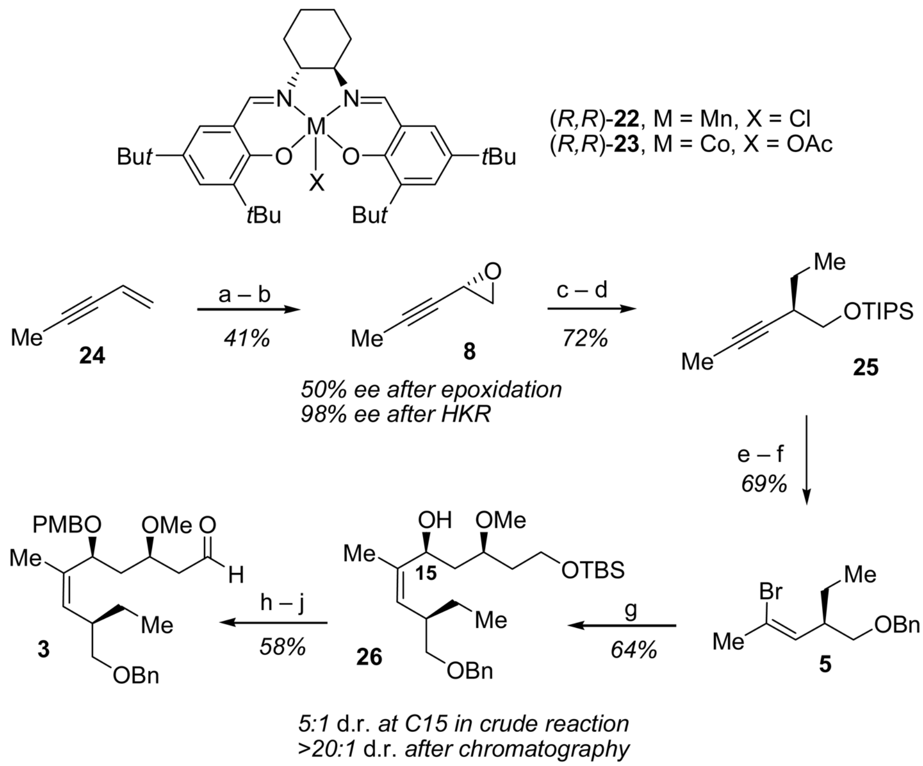


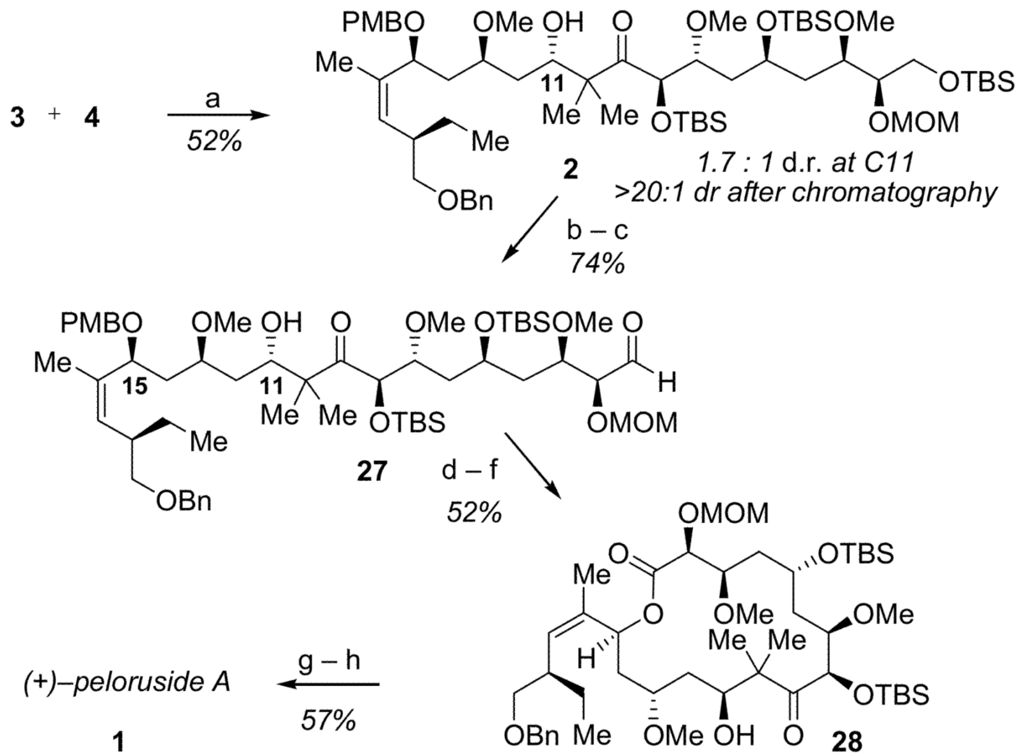
Scheme 3.

Elaboration of the hetero-Diels–Alder adduct **7** to enone **4**. Reagents and conditions: a) Pd/C, *i*-PrOH, pH 7 buffer, H_2 (200 psi), 48 h; b) KBr, TEMPO, NaOCl, pH 7 buffer, CH_2Cl_2, 0 °C, 90 min; c) *N*,*O*-dimethylamine hydrochloride, $AlMe_3$, toluene, −10 °C, 90 min; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; e) isopropenyl-magnesium bromide, THF, 5 h; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C, 4 h. TEMPO=,2,6,6-Tetramethylpiperidine-1-oxyl (free radical), THF=tetrahydrofuran, TBSOTf=*t*-butyldimethylsilyl trifluoromethanesulfonate.



Scheme 4.

Synthesis of key aldehyde fragment **3**. Reagents and conditions: a) **22** (5.0 mol%), NaOCl, CH_2Cl_2, 0 °C, 6.5 h;b) **23** (0.50 mol%), H_2O, Et_2O, 0 °C to rt, 24 h; c) ethylmagnesium chloride, THF, −78 °C to rt, 4 h; d) TIPSCl, imidazole, DMF, rt, 16 h; e) catecholborane, 40 to 50 °C, 48 h; then bromine, CH_2Cl_2, −78 °C, 10 min.; then TBAF, THF, 40 °C, 2.5 h; f) 2-benzyloxy-1-methylpyridinium triflate, MgO, trifluorotoluene, 83 °C, 24 h; g) *sec*-butyllithium, THF, Et_2O, −78 °C; then **16**, THF, −78 °C to rt, 16 h; h) PMBBr, NaH, DMF, rt, 2 h; i) acetic acid, H_2O, THF, rt, 16 h; j) Dess–Martin periodinane, CH_2Cl_2, rt, 4 h. TBAF=tetrabutylammonium fluoride, TIPSCl=triisopropylsilyl chloride, PMBBr=*p*-methoxybenzyl bromide.



Scheme 5.

Synthesis of (+)-peloruside A. Reagents and conditions: a) L-Selectride, THF, −78 °C, 2 h; then −40 °C, 2 h; b) HF·pyridine, pyridine, THF, 0 °C to rt, 2 h; c) bis-acetoxyiodobenzene, TEMPO, CH_2Cl_2, rt, 16 h; d) $NaClO_2$, NaH_2PO_4, isoamylene, H_2O, *t*-BuOH; e) DDQ, pH 7 buffer, CH_2Cl_2, 5 h; f) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, rt, 16 h; then DMAP, toluene, 60 °C, 48 h; g) Pd/C, formic acid, EtOAc, MeOH, rt, 1 h; h) 1N HCl, THF, rt, 16 h; then 4 N HCl, THF, rt, 3.5 h. DDQ=2,3-dichloro-5,6-dicyano-1,4-bezoquinone, DMAP=4-(dimethylamino)pyridine.

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